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Abstract: OPINION STATEMENT: Primary central nervous system lymphoma is a particular challenge in clinical neuro-oncology. In contrast to most other malignant brain tumors, it may be considered a curable disease at least in younger patients who can tolerate intensive treatment regimens. Yet, therapeutic progress has been limited with little measurable improvement in outcome over the last two decades, mainly due to the low incidence of this tumor, which impedes the execution of large randomized clinical trials, and the failure of most large cooperative groups to conduct such trials. Whenever possible, high-dose methotrexate (HD-MTX) is the backbone of the therapeutic regimen. Response rates can be increased by the addition of second agents like ifosfamide or cytarabine, however, their impact on overall survival is less clear. Similarly, the use of the anti-CD20 antibody rituximab, commonly used in the treatment of B cell lymphomas outside the CNS, remains controversial and has not been examined in adequate clinical trials. The prognosis of patients, who do not qualify for HD-MTX-based chemotherapy, is considerably poorer. Radiation therapy is an active treatment with high response rates but does typically not result in long-lasting remissions. It remains an important therapeutic option as a salvage therapy in patients progressing on or no longer responding to HD-MTX-based treatment. The combination of HD-MTX and radiation therapy does not prolong overall survival. It is associated with significant neurotoxicity, and it should be avoided. Another matter of debate is whether consolidation therapy by other means, such as high-dose chemotherapy followed by stem cell support, is the most promising regimen. Given these numerous uncertainties, neuro-oncologists should strive for a treatment of PCNSL patients within clinical trials to allow for the development of improved therapeutic regimens.

DOI: https://doi.org/10.1007/s11940-013-0277-y

SPRINGERLINK HEADER:

NEURO-ONCOLOGY (R SOFFIETTI, SECTION EDITOR)

Treatment of Primary CNS Lymphoma

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Running title: Therapeutic management of PCNSL

Keywords: Primary CNS lymphoma; Chemotherapy; Methotrexate; Rituximab; Temozolomide; Irradiation; Neurotoxicity; Treatment; Steroids; Intrathecal therapy

Opinion statement

Primary central nervous system lymphoma is a particular challenge in clinical neurooncology. In contrast to most other malignant brain tumors, it may be considered a curable disease at least in younger patients who can tolerate intensive treatment regimens. Yet, therapeutic progress has been limited with little measurable improvement in outcome over the last two decades, mainly due to the low incidence of this tumor which impedes the execution of large randomized clinical trials, and the failure of most large cooperative groups to conduct such trials. Whenever possible, high-dose methotrexate (HD-MTX) is the backbone of the therapeutic regimen. Response rates can be increased by the addition of second agents like ifosfamide or cytarabine, however, their impact on overall survival is less clear. Similarly, the use of the anti-CD20 antibody rituximab, commonly used in the treatment of B cell lymphomas outside the CNS remains controversial and has not been examined in adequate clinical trials. The prognosis of patients, who do not qualify for HD-MTX-based chemotherapy, is considerably poorer. Radiation therapy is an active treatment with high response rates, but does typically not result in long-lasting remissions. It remains an important therapeutic option as a salvage therapy in patients progressing on or no longer responding to HD-MTX-based treatment. The combination of HD-MTX and radiation therapy does not prolong overall survival, is associated with significant (neuro-)toxicity and should be avoided. Whether consolidation therapy by other means such as high-dose chemotherapy followed by stem cell support is the most promising regimen, is another matter of debate. Given these numerous uncertainties, neuro-oncologists should strive for a treatment of PCNSL patients within clinical trials to allow for the development of improved therapeutic regimens.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare extranodal form of Non-Hodgkin lymphoma (NHL). Registry data from the United States report that only 2.2% of all intracranial tumors are lymphomas [1]. Immunodeficiency (e.g. congenital or acquired such as human immunodeficiency virus [HIV] infection) is associated with an increased risk for the development of PCNSL. The improvement of antiretroviral therapy resulted in a decreased incidence of PCNSL in immunocompromised patients translating in fewer young patients affected with PCNSL. This contrasts a continued increase in men and women aged 65 and older for reasons yet to be determined [2]. In immunocompetent patients the median age at diagnosis is about 60 years.

PCNSL can involve all parts of the CNS including supra- and infratentorial compartments, spinal cord, meninges and cerebrospinal fluid (CSF). Finally, intraocular manifestation, either alone, then referred to as primary intraocular lymphoma (PIOL) or often associated with CNS involvement can occur. Patients with PCNSL may present with various clinical symptoms and signs. The extent of personality changes, cognitive disturbances and focal neurological deficits will depend on tumor size, localization and extent of the peritumoral edema. Intraocular involvement may cause blurred vision or other complaints.

Computed tomography (CT) or preferentially magnetic resonance imaging (MRI) are used as imaging techniques with single or multiple supratentorial homogeneous contrast-enhancing tumor masses as a typical finding [3]. There are no specific features, which allow a reliable differentiation between PCNSL and other primary or secondary brain tumors as well as inflammatory lesions. The use of ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles may improve the MRI diagnosis of PCNSL [4]. This technique, however, has not yet entered the clinical routine examination. Similarly, the value of positron emission tomography (PET) imaging using different tracers such as ^{18}F-fluordeoxyglucose (^{18}F-FDG) or ^{11}C-methionine for the diagnosis and monitoring of PCNSL has remained questionable [5-7]. Upon diagnosis of a lymphoma in the CNS, the diagnosis of PCNSL can only be rendered after exclusion of tumor manifestations outside the CNS. The detection of lymphoma cells in the CSF, also referred to as meningeal dissemination, or in the eye and cranial nerves is still compatible with PCNSL. However, staging is recommended in every patient to exclude other lymphoma manifestations [8]. This is typically done by chest, abdomen and pelvis CT. Whether FDG-PET-based visualization results in increased sensitivity remains unclear [9]. Ocular

infiltration must be ruled out by an appropriate ophthalmologic diagnostic. Vitrectomy followed by histopathological assessment of the aspirate is used to definitely verify or exclude lymphoma manifestations in the eye [10]. Bone marrow diagnostics may reveal the presence of tumors cells which, however, does not change the therapeutic approach in the absence of other systemic lymphoma manifestations [11]. Further recommendations of the International Extranodal Lymphoma Study Group (IELSG) include a lumbar puncture followed by CSF examination and testicular ultrasound in older men to exclude the presence of testicular lymphoma metastatic to brain [8].

Histopathological assessment of PCNSL tissue results in the diagnosis of a diffuse large B cell lymphoma (DLBCL) in about 90% of all patients. These tumors typically express the B cell marker CD20, a prerequisite for consideration of treatment with the monoclonal antibody rituximab (see below). Standard cytology from body fluids such as vitreous or CSF may be broadened using flow cytometry analysis as well as PCR diagnostics of the rearranged immunoglobulin heavy-chain genes. Histopathological features as well as pitfalls in the diagnosis of PCNSL have been reviewed elsewhere [12]. CNS lymphoma with a histological diagnosis other than DLBCL is rare, including low-grade lymphomas and lymphomas of T cell origin as very uncommon findings [13, 14].

Because of the variable course of the disease, several attempts have been made to group patients into different clinical prognostic groups which may help to estimate the clinical evolution. The “Memorial Sloan-Kettering Cancer Center prognostic model” published in 2006 is based on a large cohort of PCNSL patients [15]. Patients being younger than 50 years had by far the best outcome. In the group of patients aged 50 or older, the performance status allowed for further separation between 2 groups with patients being 50 years or older and a Karnofsky performance status (KPS) below 70 having the worst prognosis. A more comprehensive prognostic score was proposed by the IELSG using not only age and performance status but also elevated lactate dehydrogenase (LDH) and CSF protein levels as additional parameters which are associated with poor outcome [16]. Furthermore, the involvement of “deep brain structures” was determined as a negative factor and included in the prognostic assessment. This allowed for a separation of 3 patient groups which differ in their prognosis.

TREATMENT

Similar to many other brain tumors, the available treatment modalities for PCNSL comprise surgery, irradiation and chemotherapy, with a clear focus on the latter 2 options. The agents or regimens (e.g. CHOP) commonly used to treat systemic lymphoma have no or only marginal activity in PCNSL [17]. There are probably several reasons including different biological properties of the tumors cells and the presence of the blood-brain barrier that impedes the penetration of many chemotherapeutics into the brain. Despite some progress within the last years, many important questions regarding the most effective treatment for PCNSL remain still under debate. The rarity of PCNSL precludes the rapid execution of well-designed clinical trials with reasonable patient numbers and does not allow for rapid evaluation of different treatment regimens. Still, the publication of 2 larger randomized trials within the last years has shown that such studies are feasible and should be pursued within the next years [18, 19].

Surgery

The intention of surgery has been purely diagnostic for decades. However, an unplanned subgroup analysis of the G-PCNSL-SG1 dataset, comprising several hundred patients, revealed that complete resection may be associated with a better outcome [20]. These findings are in contrast to very small and older retrospective series that suggested a biopsy-only approach. However, surgical techniques have improved and intra-operative imaging including ultrasound and MRI has advanced which might be the reason for this observation. Obviously, there will never be a randomized clinical trial comparing resection with biopsy in patients with lesions suspicious for a cerebral lymphoma. Therefore, based on the currently available evidence, complete resection should be considered in case of single lesions which may be removed safely. In case of multiple lesions or localization of the tumor mass in an eloquent region of the brain, open or stereotactic-guided biopsy will remain the gold standard because of the overall low risk of complications of such a procedure.

Radiation therapy

Radiation therapy has been used for decades for the treatment of PCNSL, but its role has been diminishing over the last years. Treatment of PCNSL has traditionally been

considered to require the whole brain as the target volume (WBRT). Standard WBRT doses are typically 40-50 Gray (Gy) with single fractions of not more than 2 Gy. Administration of higher doses does not result in prolonged disease control, but causes more neurotoxic side effects [21]. Trials which assessed radiotherapy compared with supportive care do not exist but there is no doubt that WBRT is active against PCNSL. However, although high response rates can be achieved, they are commonly short-lasting. Furthermore, there has been increasing evidence that irradiation is associated with considerable neurotoxicity, particularly in combination with MTX-based chemotherapy and in elderly patients [22]. Major questions which have been addressed, but only partially resolved within the last years included the following:

- Is there any role for dose-reduced irradiation?
- Does consolidating radiation therapy after MTX-based chemotherapy prolong progression-free (PFS) and overall survival (OS)?
- When irradiation is deferred in patients who achieve a complete remission (CR) by chemotherapy alone, is it still active as a salvage treatment?

Several analyses indicate that the addition of WBRT to HD-MTX is associated with a considerable risk of cognitive impairment. In contrast, a profoundly lower incidence of neurotoxic effects is observed when HD-MTX was applied alone [23, 24]. Because of these problems, the concept of dose-reduced WBRT was developed aiming at avoiding cognitive side effects, but still being active as consolidation. A report by Shaw and colleagues indicated a lack of neurocognitive decline when patients received consolidating WBRT with 23.4 Gy in 1.8 Gy/fraction after HD-MTX-based chemotherapy [25]. Owing to the lack of a control group, a benefit of the consolidation treatment could not be determined. However, because of the futility of (higher) standard dose WBRT to prolong OS following MTX-based chemotherapy in the G-PCNSL-SG1 trial (see below), it can be anticipated that RT with a decreased dose will not provide more benefit in terms of survival unless an unusual dose response relationship of RT for PCNSL was postulated. When RT is deferred it is still active in the situation of tumor recurrence. A retrospective case collection comprising 48 patients demonstrated an overall response rate of 79% and a median OS of 16 months [26] suggesting that WBRT is an active treatment for patients with recurrent or refractory PCNSL.

Chemotherapy

Chemotherapy is regarded the treatment of first choice for patients newly diagnosed with PCNSL. Chemotherapy-only approaches can result in high response rates and, even more important, long-lasting remissions. There is a debate, however, on the most active compounds to be added to the established backbone of high-dose (HD)-MTX chemotherapy. The lack of benefit from many drugs which are used for the treatment of systemic lymphoma including the CHOP regimen is most likely due to their insufficient penetration of the blood-brain barrier [27].

Methotrexate alone or in combination

MTX doses that are commonly administered are in the range of 3 to 8 g/m^2, typically infused over 3 hours in 2 week-intervals. Doses less than 3 g/m^2 are probably too low to reach sufficient concentrations in the CSF to kill lymphoma cells [28, 29]. A dose of 8 g/m^2 MTX was frequently associated with the need for a dose reduction during the course of the treatment, mostly due to renal toxicity [30, 31]. Therefore, most investigators chose a dose of MTX in the range of 3-4 g/m^2 for combined therapeutic approaches with additional drugs. Various combinations of MTX with other agents have been evaluated within the last 3 decades. However, the design of these corresponding reports, commonly either from retrospective case collections and limited size or both, and the data from few uncontrolled, but at least prospective series does not allow for final conclusions and precludes definition of a standard of care beyond HD-MTX (reviewed in [32]). In fact, there are only 4 randomized trials in PCNSL of which one was closed early for poor patient accrual. Drugs which have been frequently used in combination with MTX include cytarabine, ifosfamide, temozolomide, procarbazine, vincristine and rituximab. Various regimens have been assessed aiming at increasing response rates and duration of response. The only randomized trial comparing MTX alone (3.5 g/m^2) with MTX (3.5 g/m^2) plus high-dose cytarabine (four cycles of 2 g/m^2) followed by WBRT as consolidation treatment in both arms demonstrated a superior response rate to the chemotherapy part in the MTX/cytarabine arm (CRR= 46%) compared to only 18% in the cohort of patients receiving MTX alone [19]. The disappointingly and exceptionally poor results of the single agent MTX are likely due to the fact that MTX was administered only every 3 weeks rather than the usual every 2 weeks, leading to a decreased and insufficient dose intensity. This is also reflected by the fact that only 15% of the patients in the MTX only arm experienced grade 3/4 hematological toxicity. There was also a trend towards prolonged survival with the combination (3 year OS: 46% vs. 32%). An analysis of the G-PCNSL-SG1 trial indicates that increased response rates do not

necessarily translate into prolonged OS. In this study, the addition of ifosfamide to HD-MTX resulted in increased CR rates but no superiority in terms of OS compared to HD-MTX alone was observed. In line with these findings, a comprehensive Cochrane database review concluded that the addition of other drugs to MTX may result in increased response rates as well as prolonged PFS whereas the benefit on OS remains unclear. In contrast, toxicity is significantly higher with combined treatment regimens [33]. Therefore, randomized trials with higher patient numbers and longer follow-up are required to ultimately determine the benefit from polychemotherapy as opposed to HD-MTX alone.

Chemotherapy and additional radiotherapy

Consolidating radiation therapy has been explored as an adjunct to chemotherapy for at least 20 years. There are numerous uncontrolled phase II studies exploring MTX-based regimens with additional WBRT resulting in variable response rates and survival data. These trials cannot be compared to each other because of their different designs [34-37]. However, it became clear that the addition of WBRT to chemotherapy is associated with considerable (neuro-)toxicity, particularly in elderly patients. Only in 2010, the results of the randomized G-PCNSL-SG1 trial which enrolled more than 500 patients with newly diagnosed PCNSL were published [18]. The addition of WBRT to MTX-based chemotherapy resulted in prolonged PFS (18 months for the WBRT group versus 12 months for patient who did not receive WBRT) whereas no difference in OS was observed (32 and 37 months, respectively). The trial was criticized for the long time needed for patient accrual, the high number of patients lost to follow-up and specifically the fact that approximately 1 in 4 patients did eventually not adhere to the randomization result, an inherent problem if patients are randomized several months prior to the timepoint where randomization becomes effective. However, the *per-protocol* as well as the *intention-to-treat* analysis yielded similar results for the major outcome measures, indicating that irradiation can be deferred until relapse after MTX-based first-line therapy. WBRT retains its role as a valuable treatment option in patients who fail to respond sufficiently to initial chemotherapy or do not qualify for MTX-based treatment, but outcome in relapsed PCNSL is commonly poor and long-term survival after WBRT would likely to be long-term survival with cognitive impairment.

Other approaches for consolidation therapy

Because of the failure of WBRT to prolong OS when used as a consolidation treatment and the significant long-term toxicity associated with its administration, other strategies aiming at avoiding immediate irradiation have been evaluated. One of the most promising approaches is high-dose chemotherapy (HDC) with subsequent autologous stem cell transplantation (ASCT), while omitting WBRT. This concept that has emerged over the last 15 years may be a promising strategy, in particular for younger and fit patients. HDC followed by ASCT has been examined in relatively small and uncontrolled trials both in patients with newly diagnosed as well as refractory and recurrent PCNSL. Various conditioning therapies have been used including a combination of thiotepa together with busulfane or carmustine (BCNU) or the BEAM regimen (carmustine, etoposide, cytarabine, melphalan). Several smaller trials combined a HDC approach with additional irradiation yielding excellent survival results that, however, might be compromised by late neurotoxicity, again [38-40]. Overall, MTX-based chemotherapy followed by high-dose therapy with carmustine and thiotepa and subsequent ASCT with or without WBRT resulted in promising long-term survival with a 5-year OS of 70% [41]. Further studies reported promising results without significant neurotoxicity when HDC and subsequent ASCT were administered without additional WBRT [42-44].

Another approach assessed induction chemotherapy with MTX, temozolomide and rituximab followed by consolidation with etoposide and high-dose cytarabine for patients who achieved stable disease or better after induction. The 2-year OS was 58% when all patients were analyzed and 93% in the cohort of patients who had qualified for and received consolidation therapy with etoposide and cytarabine without evidence of neurotoxicity [45]. This regimen was further evaluated within a multicenter study resulting in survival curves which display evidence of a plateau. The median OS had not yet been reached after a median follow-up of 4.9 years [46]. These results indicate that chemotherapy alone can result in excellent long-term survival. However, the potential benefit of polychemotherapy and HDC/ASCT compared to standard chemotherapy alone needs to be confirmed in randomized trials.

Other drugs

In contrast to the unquestionable importance of MTX as the backbone of any first-line regimen, it is much less clear which other agents should be used in case of tumor recurrence, absence of response or for patients who cannot tolerate HD MTX. In the following section we summarize some of the drugs that are frequently used either alone or as part of combined regimens.

Steroids

Similar to other brain tumors, The administration of corticosteroids results in a reduction of the peritumoral edema [47]. However, steroids also have a transient direct anti-tumor effect against lymphoma cells through induction of apoptosis which can result in a rapid decrease of the size of the tumor mass. When steroids are administered before surgery, they may preclude histological confirmation of the diagnosis

Rituximab

The putative beneficial role of rituximab, a monoclonal antibody targeting the cell surface antigen CD20 which is found in the majority of PCNSL, remains a matter of debate. Being part of most therapeutic regimens against systemic B cell lymphomas, its activity against lymphomas in the CNS is doubtful. CSF levels of rituximab after systemic application are approximately 0.1% of serum levels, a phenomenon which is mainly caused by the presence of the blood-brain barrier which hampers the penetration of the antibody into the CSF [48]. Still, monotherapy with rituximab in the setting of recurrent PCNSL was reported to yield occasional radiographic responses in up to 33% of patients without major toxicity concerns [49]. This may reflect the partially disrupted blood-brain barrier in PCNSL which may still allow the antibody reaching some of brain lymphoma cells. Series looking at the efficacy of rituximab when added to a MTX-based regimen suggest a certain activity in PCNSL which is associated with increased CR rates that may eventually translate into prolonged OS without adding significant toxicity [50, 51]. However, these studies have limited value due to their retrospective nature. The results of the ongoing prospective HOVON 105 (EudraCT no. 2009-014722-42) and IELSG32 (NCT01011920) trials which explore the activity of rituximab in a randomized fashion need to be awaited. Similarly, the role of intrathecal administration of rituximab has not yet been determined (see below).

Temozolomide

Temozolomide crosses the blood-barrier and has been included in several MTX-based regimens (see above). It has been mainly examined in patients with recurrent PCNSL who had previously been treated with MTX. Here, single-agent temozolomide was typically well tolerated whereas its activity was overall limited with CR rates in the range of 20-30% [52, 53]. Temozolomide alone, when used as first-line therapy in elderly patients who did not qualify for MTX-based chemotherapy had also only modest activity (see below). The efficacy of temozolomide may depend on the activity of the DNA repair protein O^6-methylguanine DNA methyltransferase (MGMT). In retrospective series, low MGMT protein expression examined by immunohistochemistry or high *MGMT* promoter methylation determined by methylation-sensitive high resolution melting (HS-HRM) analysis were predictive for response to temozolomide [54, 55]. However, larger series examining the predictive or prospective value of the MGMT status in PCNSL are lacking.

Topotecan

Topotecan is a topoisomerase I inhibitor that has been administered to patients with recurrent or MTX-refractory PCNSL. Treatment with topotecan can induce considerable response rates but may be associated with significant toxicity [56, 57].

Intrathecal therapy

Dissemination of lymphoma cells into the CSF is a common finding although the reported incidence rates are varying most likely due to different methods that were applied for the detection of meningeal affection. The presence of lymphoma cells in the CSF is probably not a negative prognostic marker [58]. Still, appropriate treatment of the CSF may be a prerequisite for long-lasting remissions. MTX administered at doses of 3 g/m^2 or higher will adequately penetrate through the blood-brain barrier to yield therapeutic CSF levels [59]. Therefore, intrathecal therapy is not considered as a standard of care which is supported by 2 retrospective analyses suggesting that additional intrathecal treatment does not result in prolonged OS compared to patient cohorts that were not treated intrathecally [60, 61]. In contrast, very promising results of a trial using a polychemotherapy approach including intraventricular therapy with MTX, prednisolone, and cytarabine were not reproduced when the intrathecal treatment was omitted [62-64].

Intraventricular administration of rituximab has been examined in a small cohort of PCNSL patients. The drug was well tolerated but the beneficial effects of this approach remain elusive [65]. Application of drugs by an Ommaya reservoir or a similar device are frequently associated with infectious complications and require an additional surgical procedure. This may be circumvented by the repeated application of drugs by lumbar puncture which, however, may not result in an equal distribution of the compound in the CSF. Whether the addition of lumbar or intraventricular treatment to MTX-based protocols results in prolonged OS needs further investigation and should be assessed within appropriate clinical trials.

Elderly patients

Patients over age 60 are commonly referred to as “elderly”. However, some studies focusing on elderly patients only include patients who are at least 65 or even 70 years old. Owing to this variability it becomes difficult to compare different studies enrolling elderly patients. As with younger patients, MTX should be the backbone of any treatment concept in elderly patients because of the lack of drugs with similar activity. In the elderly, HD-MTX is commonly well tolerated and can be safely administered in most patients [66]. Even in patients aged 80 and older, the application of MTX-containing regimens was feasible and resulted in long-term survival in some patients [67]. However, exceedingly high serum MTX levels, determined by area under the curve (AUC) calculation, are associated with reduced survival and should be avoided [68]. Promising CR rates can be achieved in elderly patients. However, the durability of these responses is reduced compared to younger patients indicating that consolidation is required in elderly patients in CR [66]. Again, various compounds have been added to MTX and assessed in smaller trials. The combination of MTX with procarbazine and lomustine resulted in a median OS of 15.4 months [69] which was only moderately changed to 17.5 months when rituximab was added in a subsequent trial [70]. A polychemotherapy regimen and additional intrathecal chemotherapy yielded a median OS of 14.3 months in a study with 50 PCNSL patients who had a median age of 72 years [71]. The combination of HD-MTX with temozolomide was reported to be well tolerated and resulted in an OS of 25 months [72]. However, a randomized phase II study comparing 2 different MTX-based regimens suggests higher activity of MPV-A (MTX, procarbazine, vincristine and cytarabine) compared to MTX combined with temozolomide [73]. This trial, however, was not designed to prove superiority and these results must be

confirmed in a phase III trial. No convincing treatment strategies are available for elderly patients who cannot be treated with HD-MTX. Radiation therapy is active but has several limitations as described above. Dose-intensified temozolomide alone has only limited efficacy [74]. In summary, similar to younger patients, HD-MTX should be used in the elderly whenever possible and considered appropriate. The benefit of further agents that are added to MTX remains to be determined.

Recurrent or refractory PCNSL

In the situation of recurrent or refractory PCNSL, no standard treatment has been defined. Several options are available and the parameters which should be taken into account include the performance status of the patient, benefit from prior therapies and the interval between last treatment and tumor recurrence. MTX re-challenge is generally considered promising in patients who achieved a CR upon MTX-based treatment [75]. In contrast, patients whose tumors must be considered refractory to MTX should be offered an alternative treatment. Here, various approaches have been assessed. Similar to the situation of newly diagnosed PCNSL, the quality of the available studies is rather poor and randomized trials are lacking. WBRT is an active treatment in the setting of recurrent PCNSL with high response rates which, however, frequently do not translate into long-lasting remissions [26, 76]. Temozolomide alone is well tolerated but has only modest activity [53]. The combination of temozolomide and rituximab was examined within a trial that was closed prematurely after a preliminary analysis had suggested disappointing activity [77]. Novel approaches include the administration of pemetrexed, a folate antimetabolite. In patients with relapsed or refractory PCNSL, it had single-agent activity but was also associated with considerable toxicity [78, 79]. Larger trials are required to determine the value of pemetrexed in PCNSL in more detail. Finally, HDC with subsequent ASCT may be a promising option for selected patients with recurrent PCNSL who qualify for such an intense and rather toxic approach [80, 81].

Compliance with Ethics Guidelines

Conflict of Interest

Patrick Roth has served as a consultant for Roche, Merck Sharp & Dohme, and Molecular Partners.

Roger Stupp has served as a consultant for Merck KGaA, Merck Sharp & Dohme/Merck & Co., and Genentech/Roche.

Michael Weller has served as a consultant for MagForce AG; has received grant support from Merck Serono, Roche, Antisense Pharma, and Bayer; and has received honoraria from Roche, Merck Serono, and Merck Sharp & Dohme.

Günter Eisele declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors for the preparation of this manuscript.

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